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Different Biosynthetic Pathways to Fosfomycin in *Pseudomonas syringae* and *Streptomyces* Species

Seung Young Kima, Kou-San Jua, William W. Metcalfa, Bradley S. Evansa, Tomohisa Kuzuyamab and Wilfred A. van der Donka,c

ABSTRACT

Fosfomycin is a wide-spectrum antibiotic that is used clinically to treat acute cystitis in the United States. The compound is produced by several strains of streptomycetes and pseudomonads. We sequenced the biosynthetic gene cluster responsible for fosfomycin production in Pseudomonas syringae PB-5123. Surprisingly, the biosynthetic pathway in this organism is very different from that in Streptomyces fradiae and Streptomyces wedmorensis. The pathways share the first and last steps, involving conversion of phosphoenolpyruvate to phosphonopyruvate (PnPy) and 2-hydroxypropylphosphonate (2-HPP) to fosfomycin, respectively, but the enzymes converting PnPy to 2-HPP are different. The genome of P. syringae PB-5123 lacks a gene encoding the PnPy decarboxylase found in the Streptomyces strains. Instead, it contains a gene coding for a citrate synthase-like enzyme, Psf2, homologous to the proteins that add an acetyl group to PnPy in the biosynthesis of FR-900098 and phosphinothricin. Heterologous expression and purification of Psf2 followed by activity assays confirmed the proposed activity of Psf2. Furthermore, heterologous production of fosfomycin in Pseudomonas aeruginosa from a fosmid encoding the fosfomycin biosynthetic cluster from P. syringae PB-5123 confirmed that the gene cluster is functional. Therefore, two different pathways have evolved to produce this highly potent antimicrobial agent.